

# **RRP Medical Reference Service**

**An RRP Foundation Publication**

**edited by**

**Dave Wunrow and Bill Stern**

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**Volume 9 • Number 2**

## Preface

The *RRP Medical Reference Service* is intended to be of potential interest to RRP patients/families seeking treatment, practitioners providing care, micro biological researchers as well as others interested in developing a comprehensive understanding of recurrent respiratory papillomatosis.

This issue focuses on a selection of references with abstracts from recent (2002 and later) RRP related publications. These listings are sorted in approximate reverse chronological order as indicated by the "Unique Identifier" numbers. Each listing is formatted as follows:

Journal or reference  
Title  
Language (if it is not specified assume article is in English)  
Author(s)  
Primary affiliation (when specified)  
Abstract  
Unique identifier

If copies of complete articles are desired, we suggest that you request a reprint from one of the authors. If you need assistance in this regard or if you have any other questions or comments please feel free to contact:

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## **RRPF Selected Articles and Abstracts**

*Virus Res 2002 Nov;89(2):275-84*

### **The status of HPV16-specific T-cell reactivity in health and disease as a guide to HPV vaccine development.**

Van der Burg SH, de Jong A, Welters MJ, Offringa R, Melief CJ.

Tumor Immunology Group, Department of Immunohematology and Blood Transfusion, University Medical Center, Albinusdreef 2, 2333 ZA, Leiden, The Netherlands

Human papilloma viruses (HPV) are among the most common sexually transmitted pathogens in young adults. In the majority of individuals, anti-viral immunity is capable of suppressing viral infection but in a minority of patients viral infection is not cleared in time to prevent the development of malignancies. In these cases, HPV16-specific immunity may develop too late, is not strong enough, and/or is possibly of the wrong type. The influence of pre-existing immunity on the efficacy of vaccines is largely unknown. Nor has it been studied what the effect is of vaccines on the various types of pre-existing HPV-specific T-cell immunity. Animal models showing that vaccines are able to protect against a subsequent tumor challenge and even to treat transplantable tumors, are not qualified to address this point because tumor development is not preceded by persistent viral infection. Therefore, the comparison between fully characterized pre-existing HPV-specific immunity in patients and healthy subjects is a prerequisite for the full appreciation of vaccine-efficacy as well as for further development of next-generation vaccines.

Unique Identifier: 22337978

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*Virus Res 2002 Nov;89(2):183-90*

### **The viral etiology of cervical cancer.**

Bosch FX, Munoz N.

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Epidemiological studies supported by molecular technology have provided sufficient evidence on the causal role of some Human Papillomavirus (HPV) infections in the development of cervical cancer. This association has been evaluated under all proposed sets of causality criteria and endorsed by the scientific community and major review institutes. HPV has been proposed as the first-ever identified, necessary cause of a human cancer. In practical terms, the concept of a necessary cause

implies that cervical cancer does not and will not develop in the absence of the persistent presence of HPV-deoxyribonucleic acid (DNA). This important advancement has two practical implications in prevention. Firstly, screening programs can be enhanced if HPV testing is judiciously incorporated into solving the fraction of ambiguous cytology readings. In some populations HPV screening as a primary test may prove to be the strategy of choice. Secondly, like in the hepatitis B disease model, intense efforts are currently being put into the development and testing of vaccines that may prevent the relevant HPV infections, and presumably, cervical cancer. At this stage of development, regulatory agencies are requested to evaluate the scientific evidence and weigh its implications in relation to costs, public health investments and policy. This is a subjective evaluation that could be guided by a careful description of the most relevant studies and findings.

Unique Identifier: 22337969

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*J Nutr* 2002 Nov;132(11):3314-24

### **Diindolylmethane alters gene expression in human keratinocytes in vitro.**

Carter TH, Liu K, Ralph W Jr, Chen D, Qi M, Fan S, Yuan F, Rosen EM, Auburn KJ.

North Shore-Long Island Jewish Research Institute, Manhasset, NY 11030, USA.

Indole-3-carbinol (I3C) and its dimer 3,3'-diindolylmethane (DIM), obtained from dietary consumption of cruciferous vegetables, have multiple biochemical activities. Both compounds have been effective clinically in treating precancerous lesions of the cervix and laryngeal papillomas, pathologies with a human papillomavirus (HPV) component. Using cDNA microarrays, we examined early changes in gene expression after treatment with 100 micro mol/L DIM in C33A and CaSki cervical cancer cells and in an immortalized human epithelial cell line (HaCat), as well as in normal human foreskin keratinocytes (HFK). Multiple analyses were done after treating C33A cells for 6 h; other analyses included 4- and 12-h treatments of C33A and 6-h treatments of CaSki, HaCat and HFK cells. DIM consistently altered the expression of >100 genes at least twofold. Many of the stimulated genes encode transcription factors and proteins involved in signaling, stress response and growth. Results were comparable between transformed cells with and without integrated HPV sequences, and many of the same genes were induced in these cancer-derived cells and in noncancer cells. Eight genes encoding bZip proteins were among the most consistently and robustly induced, including the stress-associated immediate early gene GADD153 (>50 fold in C33A) and nuclear factor-interleukin 6 (NF-IL6), also known as c/EBPbeta, (>5 fold in C33A), which has been shown to reduce expression of HPV oncogenes. Induction of GADD153, NF-IL6 and ATF3 was confirmed by Western analysis. In functional analyses, DIM not only suppressed transcription of a luciferase gene driven by the HPV11 upstream regulatory region (URR) in C33A, CaSki, HaCat and

HFK cells from >2-fold to 37-fold depending on the type of cells, but also reduced endogenous transcription of HPV16 oncogenes to undetectable levels in CaSki cells as determined by an RNase protection assay. Ectopic expression of GADD153 or NF-IL6 suppressed transcription in a dose-dependent manner driven by the HPV11 URR in C33A, CaSki, HaCat and HFK cells. These results identify unexpected ways in which dietary I3C and DIM invoke cellular responses and are consistent with a potential antiviral effect of DIM on keratinocytes, but they do not explain the differential sensitivity

Unique Identifier: 22309249

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*Srp Arh Celok Lek 2002 May-Jun;130 Suppl 1:76-9*

**[Tumors of the larynx in children]**

[Article in Serbo-Croatian (Cyrillic)]

Djukic V, Petrovic Z, Petrovic B.

Institut za otorinolaringologiju i maksilofacijalnu, hirurgiju Klinickog centra Srbije, 11 000 Beograd, Pasterova 2.

No abstract available.

Unique Identifier:22282975

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*Mini Rev Med Chem 2002 Apr;2(2):163-75*

**Highlights in the development of new antiviral agents.**

De Clercq E.

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The potential of a large variety of new compounds and new strategies for the treatment of virtually all major virus infections has been addressed. This includes, for the treatment of HIV infections, virus adsorption inhibitors (cosalane derivatives, cyanovirin-N), co-receptor antagonists (TAK-779, AMD3100), viral fusion inhibitors (pentafuside T-20, betulinic acid derivatives), viral uncoating inhibitors (azodicarbonamide), nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs: emtricitabine, amdoxovir, dOTC, d4TMP prodrugs, tenofovir disoproxil fumarate), non-nucleoside

reverse transcriptase inhibitors (NNRTIs: thiocarboxanilide UC-781, capravirine, SJ-3366, DPC 083, TMC 125/R165335), integrase inhibitors (diketo acids), transcription inhibitors (temacrazine, flavopiridol), protease inhibitors (atazanavir, mozenavir, tipranavir); for the treatment of RSV and paramyxovirus infections, viral fusion inhibitors (R170591, VP-14637, NMS03); for the treatment of picornavirus infections, viral uncoating inhibitors (pleconaril); for the treatment of pesti- (hepaci-, flavi-) virus infections, RNA replicase inhibitors (VP-32947); for the treatment of herpesvirus (HSV, VZV, CMV) infections, DNA polymerase inhibitors (A-5021, L- and D-cyclohexenylguanine); for the treatment of VZV infections, bicyclic furopyrimidine analogues; for the treatment of CMV infections, fomivirsen; for the treatment of DNA virus infections at large (papilloma-, polyoma-, herpes-, adeno- and poxvirus infections), cidofovir; for the treatment of influenza, neuraminidase inhibitors (zanamivir, oseltamivir, RWJ-270201); for the treatment of HBV infections, adefovir dipivoxil; for the treatment of HBV and HCV infections, N-glycosylation inhibitors (N-nonyl-deoxyojirimycin); and, finally, IMP dehydrogenase inhibitors and S-adenosylhomocysteine hydrolase inhibitors, for the treatment of various virus infections, including hemorrhagic fever virus infections.

Unique Identifier:22257899

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*Virology* 2002 Sep 15;301(1):176-87

**Chimeric human papilloma virus-simian/human immunodeficiency virus virus-like-particle vaccines: immunogenicity and protective efficacy in macaques.**

Dale CJ, Liu XS, De Rose R, Purcell DF, Anderson J, Xu Y, Leggatt GR, Frazer IH, Kent SJ.

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Vaccines to efficiently block or limit sexual transmission of both HIV and human papilloma virus (HPV) are urgently needed. Chimeric virus-like-particle (VLP) vaccines consisting of both multimerized HPV L1 proteins and fragments of SIV gag p27, HIV-1 tat, and HIV-1 rev proteins (HPV-SHIV VLPs) were constructed and administered to macaques both systemically and mucosally. An additional group of macaques first received a priming vaccination with DNA vaccines expressing the same SIV and HIV-1 antigens prior to chimeric HPV-SHIV VLP boosting vaccinations. Although HPV L1 antibodies were induced in all immunized macaques, weak antibody or T cell responses to the chimeric SHIV antigens were detected only in animals receiving the DNA prime/HPV-SHIV VLP boost vaccine regimen. Significant but partial protection from a virulent mucosal SHIV challenge was also detected only in the prime/boosted macaques and not in animals receiving the HPV-SHIV VLP vaccines alone, with three of five prime/boosted animals retaining some CD4<sup>+</sup> T cells following challenge. Thus, although some immunogenicity and partial protection was observed in non-human primates receiving both DNA and chimeric HPV-SHIV VLP vaccines, significant improvements in vaccine design are required before we can confidently proceed with this approach to clinical trials.

Unique Identifier: 22247914

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*J Med Invest* 2002 Aug;49(3-4):124-33

### **Human papilloma virus (HPV) and cervical cancer.**

Furumoto H, Irahara M.

Department of Obstetrics and Gynecology, The University of Tokushima School of Medicine, Japan.

Epidemiological and experimental studies have clearly shown that high-risk HPV infection is the main etiologic factor for cervical cancer. Recent studies have indicated that the E6 and E7 gene products play a critical role in cervical carcinogenesis. The E6 and E7 products interfere with the p53 and pRB functions, respectively, and deregulate the cell cycle. The HPV DNA is integrated into the host's chromosomes with disruption of the E2 gene. This disruption promotes the expression of E6 and E7, leading to the accumulation of DNA damage and the development of cervical cancer. The study of the immune response against HPV has been hampered by the lack of a cell culture system for the virus. A breakthrough was made by the discovery that a major capsid protein L1 self-assembles into virus-like particles (VLP) when expressed in eukaryotic systems. Clinical trials of VLP-based vaccines are in progress, and DNA vaccines for the HPV surface protein genes are under development. The E7 and E6 oncoproteins are attractive targets for cancer immunotherapy because their expression is required to maintain the oncogenicity of cervical cancer cells. Cancer immunotherapy for cervical cancer with vaccinations of E7 peptides or dendritic cell-based immunotherapy is moving toward clinical trials.

Unique Identifier: 22234810

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*Arch Pathol Lab Med* 2002 Oct;126(10):1184-8

### **Molecular events in the progression of recurrent respiratory papillomatosis to carcinoma.**

Lele SM, Pou AM, Ventura K, Gatalica Z, Payne D.

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slele2@uky.edu

CONTEXT: Identification of the type of human papillomavirus (HPV) by polymerase chain reaction and sequencing to determine coinfection or superinfection (by more than 1 HPV type) and other molecular events have not been reported in a series of patients exhibiting the morphologic spectrum of recurrent respiratory papillomatosis progressing to carcinoma. DESIGN: Four cases of juvenile-

onset recurrent respiratory papillomatosis progressing to carcinoma (no history of smoking or irradiation in 2 cases) were studied. Morphologically distinct foci (squamous papilloma, pulmonary papillomatosis, squamous dysplasia subjacent to carcinoma, and squamous carcinoma) were subjected to laser capture microdissection and polymerase chain reaction amplification using general primers in addition to type-specific primers for HPV types 16 and 18. Direct sequencing of polymerase chain reaction products identified the type of HPV. The tissue sections were immunostained using antibodies to p53, pRb, p21(WAF1), and p16 proteins with a semiquantitative assessment. RESULTS: Human papillomavirus 11 was the only type of HPV identified in all lesions of all cases associated with recurrent respiratory papillomatosis. There was a marked increase in p53 protein expression in foci of dysplasia and carcinoma as compared to squamous papilloma and pulmonary papillomatosis. An inverse correlation between p53 and p21(WAF1) protein expression was noted in all lesions. pRb protein expression increased from the benign to the malignant end of the spectrum. p16 protein was expressed in all lesions. CONCLUSIONS: Infection by HPV-11 may be an early event associated with progression of recurrent respiratory papillomatosis to carcinoma. Increased expression of p53 and pRb proteins and a reduced expression of p21(WAF1) protein appear to be significant subsequent events.

Unique Identifier: 22233311

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*Duodecim* 2002;118(13):1388-96

**[Papilloma viruses on the mucous membranes]**

[Article in Finnish]

Aaltonen LM, Hiltunen-Back E, Paavonen J.

HYKS:n korva-, nena- ja kurkkutautien klinikka PL 220, 00029 HUS. [leena-maija.aaltonen@helsinki.fi](mailto:leena-maija.aaltonen@helsinki.fi)

No abstract available.

Unique Identifier: 22225572

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*Vestn Otorinolaringol* 2002;(3):20-3

**[Characteristics of psychoemotional sphere in children with chronic laryngeal obstruction]**

[Article in Russian]

Shepina AI, Makarchuk AV, Soldatskii IuL, Tarabrina NV, Onufrieva EK, Shchepin NV.

45 children from 10 to 14 years of age with chronic laryngeal obstruction were examined psychologically. 29 of them had recurrent respiratory papillomatosis, 16 ones had cicatricial laryngostenosis. The majority of the examinees (65%) showed symptoms of posttraumatic stress syndrome (PTSS). The children develop PTSS one-two years after onset of laryngeal obstruction. Later, the children underwent persistent specific maladaptation personality disorders. Thus, children with recurrent laryngeal papillomatosis, especially with cicatricial laryngostenosis, should undergo psychological correction.

Unique Identifier: 22215006

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*Eye 2002 Sep;16(5):649-51*

### **Topical and intralesional interferon therapy for recurrent lacrimal papilloma.**

Parulekar MV, Khooshabeh R, Graham C.

No abstract available.

Unique Identifier: 22181332

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*Clin Otolaryngol 2002 Aug;27(4):237-43*

### **Recurrent respiratory papillomatosis.**

Shykhon M, Kuo M, Pearman K.

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Recurrent respiratory papillomatosis is a relatively rare disease caused by members of the human papilloma virus family. Lesions may occur anywhere throughout the respiratory tract but show a predilection for squamo-columnar epithelial junctions, frequently leading to hoarseness and upper airway obstruction. Rarely, it can progress to squamous cell carcinoma. The impact of recurrent respiratory papillomatosis on patients, their families, and the health care system is considerable. Unfortunately, despite extensive investigational studies, no cure is available for the disease. This article reviews the aetiology of and therapeutic options for recurrent respiratory papillomatosis.

Unique Identifier: 22159643

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*Expert Opin Investig Drugs 2002 Aug;11(8):1139-48*

**Novel treatments for recurrent respiratory papillomatosis.**

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Recurrent respiratory papillomatosis is a rare but often severe disease. Although benign in histology, epithelial proliferations may result in progressive hoarseness, stridor, obstruction of the airway and respiratory distress. The current standard of care is surgical therapy with a goal of complete removal or debulking of papillomas and preservation of normal structures. Frequent recurrences and the need for repeated surgical interventions make this treatment a frustrating experience for both the patient and the physician. Many adjuvant therapies have been investigated but no single treatment modality proved to be effective in eradicating recurrent respiratory papillomatosis. In contrast to HIV, cytomegalovirus and hepatitis B pharmaceutical research has been less successful with human papilloma virus vaccines for a variety of reasons. This review focuses on the current status of recurrent respiratory papillomatosis and on future directions of prevention and therapy.

Unique Identifier: 22146172

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*Laryngoscope* 2002 May;112(5):933-5

**Single-stage, stentless endoscopic repair of anterior glottic webs.**

Schweinfurth J.

Milton S. Hershey Medical Center, Pennsylvania State University, Hershey 17033, USA.

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No abstract available.

Unique Identifier: 22145176

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*Laryngoscope* 2002 Apr;112(4):700-7

**Human papillomavirus in larynx.**

Aaltonen LM, Rihkanen H, Vaheri A.

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**OBJECTIVES:** The core of the present clinical and basic research knowledge of laryngeal human papillomavirus (HPV) infection is described. **STUDY DESIGN:** Review. **METHODS:** A computer-aided search of MEDLINE database supplemented by hand searches of key journals was conducted. **RESULTS:** One of the tumor-promoting factors in the larynx is the HPV found both in normal laryngeal epithelium and in laryngeal tumors. The most important manifestation of laryngeal HPV infection is laryngeal papillomatosis, a rare disease caused by HPV types 6 and 11. In laryngeal carcinogenesis, the role of HPV remains uncertain. The means of transmission of HPV are partly unknown, and the course of laryngeal HPV infection is unpredictable and variable. Treatment of laryngeal papillomatosis is based on surgery, especially on CO2 laser and shaver. Alpha-interferon is the drug of choice in patients whose response to surgery is poor. However, neither interferon nor other antiviral drugs are able to eradicate the virus from laryngeal mucosa. Little is known about immunological mechanisms involved in laryngeal HPV infection, but in defense against HPV cellular immunity is considered a more important mechanism than humoral immunity. A good experimental model of HPV infection is lacking in which the entire viral life cycle can take place. Organotypic cell cultures (collagen rafts) are useful, but the rate-limiting step in this method is the difficulties in culturing HPV-positive epithelial cells. **CONCLUSIONS:** Although laryngeal papillomatosis is clinically well defined, the mechanisms and treatment modalities of laryngeal HPV infection need further investigations.

Unique Identifier: 22145070

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*Laryngoscope* 2002 Apr;112(4):696-9

### **Intralesional cidofovir therapy for laryngeal papilloma in an adult cohort.**

Bielamowicz S, Villagomez V, Stager SV, Wilson WR.

Division of Otolaryngology-Head and Neck Surgery, George Washington University, Washington, DC 20037, USA. sursxb@gwumc.edu

**OBJECTIVES:** To confirm the safety and efficacy of intralesional cidofovir in the management of laryngeal papilloma and to identify variables that correlate with number of injections needed to achieve remission. **STUDY DESIGN:** An open-trial prospective evaluation of the efficacy of intralesional cidofovir in subjects with laryngeal papilloma. **METHODS:** Fourteen adult subjects with biopsy-proven laryngeal papilloma were enrolled in a treatment study of intralesional cidofovir. Preprotocol disease duration ranged from 1 to 30 years with a mean duration of 7 years. Subjects received monthly injections of cidofovir with a maximum dose of 37.5 mg per injection in 6 cc saline (6.25 mg/mL). Injections were repeated until no papilloma could be visually identified during an intraoperative evaluation. After disease remission was achieved, subjects received an additional injection. All injections occurred during suspension microlaryngoscopy. **RESULTS:** All subjects have achieved disease remission using an injection-only treatment protocol. No additional laryngeal scarring or systemic toxicity was identified. On average, 6 injections were required to achieve remission. Preprotocol disease duration and anatomical staging correlated positively with the

number of injections required for disease remission. CONCLUSIONS: Intralesional injection of cidofovir is an excellent treatment option with limited local and systemic toxicities. The injection therapy regimen requires perseverance from both patient and surgeon. Remission of disease can be achieved in adults with laryngeal papilloma.

Unique Identifier: 22145069

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*Lancet Infect Dis 2002 Jun;2(6):353-67*

### **Therapeutic vaccination against chronic viral infections.**

Vandepapeliere P.

Clinical R&D HIV vaccines and anti-infective therapeutic vaccines, GlaxoSmithKline Biologicals, Rue de l'Institut 89, B-1330, Rixensart, Belgium. pierre.vandepapeliere@gskbio.com

Chronic viral infections such as those caused by hepatitis B virus, human papilloma virus, herpes simplex virus, and HIV, in theory, present logical targets of active specific immunotherapy. Indeed, immunological mechanisms are involved in several aspects of their pathogenesis and natural course, such as virus persistence, destruction of infected cells and control of viral replication. Therapeutic vaccination could therefore be an adequate replacement for, or adjunct to, existing therapies. Almost all approaches to therapeutic vaccination have been evaluated in those four disease areas. Despite encouraging results in animals none of these attempts has, so far, been completely successful in the human setting. However, with a better understanding of the immunological mechanisms involved in the control of disease successful therapeutic vaccines, used alone or in combination with other therapies, are an achievable goal.

Unique Identifier: 22140484

*Am J Ophthalmol 2002 Aug;134(2):268-70*

### **Treatment of conjunctival papillomata with topical interferon Alfa-2b.**

Schechter BA, Rand WJ, Velazquez GE, Williams WD, Starasoler L.

Rand Eye Institute, Pompano Beach, Florida 33064, USA.

PURPOSE: Two patients with biopsy-proven conjunctival papillomata exhibited complete resolution after treatment with topical Interferon Alfa-2b (IFNalpha2b). DESIGN: Interventional case reports. METHODS: Two patients with monocular biopsy-confirmed conjunctival papillomata were treated with IFNalpha2b, 1 million units/cc, one drop four times daily until clinical resolution was achieved. RESULTS: (Patient 1) The lesion's size was significantly reduced at 1 month. Complete resolution was noted at the 3-month visit. No recurrences were seen 40 months post-

treatment. (Patient 2) The lesion completely resolved after 6 weeks of treatment. No recurrence has occurred 18 months post-treatment. No systemic or local side effect of treatment was noted.

CONCLUSIONS: Two sizable conjunctival papillomata resolved using topical IFNalpha2b alone. Interferon is usually not considered effective for large solid tumors without surgical debulking. We realize that this is a limited case series, but these cases may serve as a basis for further investigation.

Unique Identifier: 22135123

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*Arch Otolaryngol Head Neck Surg* 2002 Jul;128(7):783-6

### **Can mumps vaccine induce remission in recurrent respiratory papilloma?**

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OBJECTIVE: To describe our experience using laser excision and locally injected mumps vaccine to induce remission in patients with recurrent respiratory papilloma (RRP). SETTING: Tertiary care regional medical center. PARTICIPANTS: Initially, 11 children with RRP treated in a pilot study with laser excision at regular intervals for at least a year without adjuvant therapy; later, a series of 18 children and 20 adults with RRP, some of whom had used various adjuvant therapy with interval laser excision. INTERVENTIONS: Both patient groups continued their same interval laser excision with the same or similar laser, same clinical setting, and same surgeon. Locally injected mumps vaccine was then administered into the excision site after each laser removal of papilloma.

OUTCOME MEASURES: Larynx and trachea were microphotographed with each treatment. Two consecutive disease-free intervals and a follow-up of at least 1 year were required criteria for remission. RESULTS: In the pilot study, remission was induced in 9 (82%) of 11 patients by 1 to 10 injections, with follow-up of 5 to 19 years. In the subsequent series, remission was induced in 29 (76%) of 38 patients by 4 to 26 injections, and follow-up was 2 to 5 years. CONCLUSIONS: Combined with serial laser excision, mumps vaccine positively influences induction of remission in children with RRP. The mechanisms of this effect are unclear, but the treatment is readily available, inexpensive, and has a low risk of adverse effects.

Unique Identifier: 22112467

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*Emerg Med J* 2002 Jul;19(4):362-5

### **Respiratory papillomatosis: a rare cause of collapse in a young adult presenting to the emergency department.**

Carroll CD, Saunders NC.

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Treating patients with rapidly deteriorating respiratory compromise in the emergency room is difficult and stressful. The patient in front of you is rapidly progressing towards total cardiorespiratory collapse and you may have no idea why. A case is reported of an adult presenting with impending cardiorespiratory collapse attributed to asthma who actually had upper airway obstruction caused by laryngeal papillomata. This case report reinforces the importance of airway assessment, gives an overview of respiratory papillomatosis, and reiterates both the non-surgical and surgical approach to the difficult airway.

Unique Identifier: 22095155

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*J Virol* 2002 Aug;76(15):7616-24

**Ubiquitin-fused and/or multiple early genes from cottontail rabbit papillomavirus as DNA vaccines.**

Leachman SA, Shylankevich M, Slade MD, Levine D, Sundaram RK, Xiao W, Bryan M, Zelterman D, Tiegelaar RE, Brandsma JL.

Department of Dermatology, School of Medicine, Yale University, New Haven, Connecticut 06520, USA.

Human papillomavirus (HPV) vaccines have the potential to prevent cervical cancer by preventing HPV infection or treating premalignant disease. We previously showed that DNA vaccination with the cottontail rabbit papillomavirus (CRPV) E6 gene induced partial protection against CRPV challenge and that the vaccine's effects were greatly enhanced by priming with granulocyte-macrophage colony-stimulating factor (GM-CSF). In the present study, two additional strategies for augmenting the clinical efficacy of CRPV E6 vaccination were evaluated. The first was to fuse a ubiquitin monomer to the CRPV E6 protein to enhance antigen processing and presentation through the major histocompatibility complex class I pathway. Rabbits vaccinated with the wild-type E6 gene plus GM-CSF or with the ubiquitin-fused E6 gene formed significantly fewer papillomas than the controls. The papillomas also required a longer time to appear and grew more slowly. Finally, a significant proportion of the papillomas subsequently regressed. The ubiquitin-fused E6 vaccine was significantly more effective than the wild-type E6 vaccine plus GM-CSF priming. The second strategy was to vaccinate with multiple CRPV early genes to increase the breadth of the CRPV-specific response. DNA vaccines encoding the wild-type CRPV E1-E2, E6, or E7 protein were tested alone and in all possible combinations. All vaccines and combinations suppressed papilloma formation, slowed papilloma growth, and stimulated subsequent papilloma regression. Finally, the two strategies were merged and a combination DNA vaccine containing ubiquitin-fused versions of

the CRPV E1, E2, and E7 genes was tested. This last vaccine prevented papilloma formation at all challenge sites in all rabbits, demonstrating complete protection.

Unique Identifier: 22092515

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*Ann Otol Rhinol Laryngol* 2002 Jun;111(6):486-92

**585-nm pulsed dye laser treatment of glottal papillomatosis.**

Franco RA Jr, Zeitels SM, Farinelli WA, Anderson RR.

Department of Otolaryngology and Laryngology, Harvard Medical School, Boston, Massachusetts, USA.

Treatment of recurrent respiratory papillomatosis of the glottis is often challenging. The surgeon and patient must cooperatively balance decisions regarding airway safety, effects of multiple general anesthetics, employment disturbance, and vocal dysfunction. A pilot study was done in 41 adult cases (23 patients; 78 vocal folds) without complication to evaluate the effectiveness of a 585-nm pulsed dye laser (PDL; 450-micros pulse width; fluence of 38 to 255 J/cm<sup>2</sup>; 1- to 2-mm spot size) in the treatment of this disorder. Thirty-seven of the 41 cases (90%) were bilateral disease. Twenty-six of the 41 cases (63%; including 20 cases with involvement of the anterior commissure) were treated by bilateral photocoagulation of the lesions' microcirculation without microflap resection of tissue. Clinical observation revealed that irradiated but unresected disease involuted without development of an anterior commissure web. In the initial 13 of the 41 cases (32%), PDL treatment was followed by cold instrument microflap resection. The PDL enhanced the epithelial excision by improving hemostasis and by creating an optimal dissection plane between the basement membrane and the underlying superficial lamina propria. The PDL at 585 nm was less effective in the management of exophytic lesions because of its limited depth of penetration (approximately 2 mm). In this initial trial, the PDL was a relatively safe and efficacious treatment for glottal recurrent respiratory papillomatosis. Since the lesions involute without complete resection of the diseased epithelium, the anterior commissure can be treated to minimize the number of procedures. To study patterns of recurrence will require longer follow-up.

Unique Identifier: 22085070

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*Otolaryngol Head Neck Surg* 2002 Jun;126(6):642-8

**Office-based treatment of laryngeal papillomatosis with percutaneous injection of cidofovir.**

Chhetri DK, Blumin JH, Shapiro NL, Berke GS.

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**OBJECTIVE:** Our aim was to report our experience with office-based treatment of severe laryngeal papillomatosis with percutaneous injection of cidofovir in a case series of 5 patients. **STUDY DESIGN AND SETTING:** We conducted a retrospective review of a case series in a tertiary academic care voice disorders clinic. Adult patients with papillomas of the vocal cords and anterior commissure received percutaneous injection using a point-touch technique. Clinical improvement or remission of the papillomatosis was noted. **RESULTS:** Before initiation of office treatments, patients required direct laryngoscopy and CO(2) laser ablation of papillomas on average every 2.8 months. There were no complications related to the injection technique. During a treatment period of 7 to 16 months (mean 12 months), a significant reduction in the volume of papillomatosis was achieved in all patients. One patient received 2 treatments and another received 1 treatment in the operating room for final clearance of papillomas. **CONCLUSION:** Office-based treatment of adult patients with anterior laryngeal papillomatosis using percutaneous injection of cidofovir reduces the need for repeated direct laryngoscopy and laser ablation under general anesthesia. **SIGNIFICANCE:** Percutaneous injection treatment with cidofovir is a useful adjunct to direct laryngoscopy and laser ablation in the treatment of laryngeal papillomatosis.

Unique Identifier: 22082356

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*Br J Cancer 2002 Jul 1;87(1):75-80*

**High-risk human papillomavirus clearance in pregnant women: trends for lower clearance during pregnancy with a catch-up postpartum.**

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We followed 353 women referred with abnormal cervical cytology in a non-intervention cohort study. In 91 pregnant women we compared high-risk human papilloma virus rates in the subsequent trimesters and postpartum in comparison to 262 non-pregnant women. High-risk human papilloma virus clearance was compared with 179 high-risk human papilloma virus positive non-pregnant women. Our main questions were: (1) do high-risk human papilloma virus rates change during pregnancy?; and (2) is there any difference between high-risk human papilloma virus clearance in pregnant and non-pregnant women? Women were monitored 3-4 monthly by cytology, colposcopy, and high-risk human papilloma virus testing. The median follow-up time was 33 months (range 3-74). Non-pregnant women showed prevalence rates of high-risk human papilloma virus of 64, 57, 53, and 50%, respectively, in four subsequent 3-months periods since the start of the study. These high-risk human papilloma virus rates were higher than in the three trimesters of pregnancy, and during the first 3 months postpartum, i.e. 50, 44, 45, and 31%, respectively. Postpartum only, this difference was statistically significant ( $P=0.004$ ). Paired comparisons of high-risk human

papilloma virus prevalence rates of the different trimesters with the postpartum rate showed (McNemar test) decreased rates: first trimester: 18% (P=0.02), second trimester: 13% (P=0.02) and third trimester: 23% (P<0.005). Such a phenomenon was not found in non-pregnant women. Pregnant women showed a trend for increased high-risk human papilloma virus clearance during the third trimester and postpartum compared to non-pregnant women (hazard ratios 3.3 (0.8- 13.7) and 4.6 (1.6- 12.8), respectively). These results suggest a lowered immune-response against human papilloma virus during the first two trimesters of pregnancy with a catch-up postpartum.

Unique Identifier: 22079132

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*Antiviral Res 2002 Jul;55(1):1-13*

### **Cidofovir in the treatment of poxvirus infections.**

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Cidofovir [(S)-1-(3-hydroxy-2-phosphonylmethoxypropyl)cytosine, HPMPC] has since 1996 been licensed for clinical use in the treatment of cytomegalovirus (CMV) retinitis in AIDS patients. Cidofovir has broad-spectrum activity against virtually all DNA viruses, including herpes-, adeno-, polyoma-, papilloma- and poxviruses. Among the poxviruses, vaccinia, variola (smallpox), cowpox, monkeypox, camelpox, molluscum contagiosum and orf have proven sensitive to the inhibitory effects of cidofovir. In vivo, cidofovir has shown high efficacy, even after administration of a single systemic (intraperitoneal) or intranasal (aerosolized) dose, in protecting mice from a lethal respiratory infection with either vaccinia or cowpox. Cidofovir has also demonstrated high effectiveness in the treatment of vaccinia virus infection in severe combined immune deficiency mice. In humans, cidofovir has been used successfully in the treatment, by both the topical and intravenous route, of recalcitrant molluscum contagiosum and orf in immunocompromised patients. Taken together, these data indicate that cidofovir should be effective in the therapy and short-term prophylaxis of smallpox and related poxvirus infections in humans, as well as the treatment of the complications of vaccinia that may arise in immunocompromised patients inadvertently inoculated with the smallpox vaccine (vaccinia).

Unique Identifier: 22071488

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*J Gen Virol 2002 Jul;83(Pt 7):1651-8*

### **PTEN is a negative regulator of STAT3 activation in human papillomavirus-infected cells.**

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Laryngeal papillomas are caused by infection of the laryngeal epithelium by human papillomavirus type 6 or type 11 (HPV-6/-11). Previous studies in our laboratory have demonstrated an increase in PI3 kinase levels in papilloma tissue. However, activation of the downstream effector of PI3 kinase, protein kinase B (PKB/Akt), was reduced. This observation was explained by the elevated expression of the phosphatase and tensin homologue (PTEN), a recently characterized tumour suppressor, in papilloma tissue. Recent investigation of the possible functional roles of PTEN during papilloma development has now indicated that the level of tyrosine(705)-phosphorylated signal transducer and activator of transcription 3 [PTyr(705)STAT3] could be inversely correlated to that of PTEN as well. In vitro phosphatase assays suggested the presence of an increased level of a PTyr(705)STAT3 phosphatase in papilloma extract. Immunodepletion of PTEN from papilloma extracts resulted in a reduction of the PTyr(705)STAT3 phosphatase activity. Transfection of PTEN cDNA into HeLa cells attenuated STAT3 phosphorylation at Tyr(705) in a dose-dependent manner. This attenuation of STAT3 phosphorylation was independent of the STAT3 kinase. Interestingly, introduction of a lipid phosphatase mutant of PTEN (G129E) resulted in heightened PTyr(705)STAT3 phosphatase activity, relative to that obtained from wild-type PTEN transfection. These data indicate that PTEN negatively regulates STAT3 activation in HPV-infected papilloma cells. Induction of PTEN and reduction of activated STAT3 might be a result of a host defence mechanism or a virus-directed strategy to alter normal epithelial differentiation programming.

Unique Identifier: 22070215

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*Vestn Otorinolaringol* 2002;(2):34-6

**[Interferon therapy and immunotherapy in children with respiratory papillomatosis]**

[Article in Russian]

Tsvetkov EA, Sel'kov SA, Chmyreva NN.

The ENT clinic of St-Petersburg Pediatric Medical Academy for 15 years admitted 126 children with respiratory papillomatosis 10 months to 15 years of age. 111 of them had laryngeal papillomatosis. The scheme of combined treatment was adjusted to interferon status of the patients. Replacement therapy with recombinant interferon--viferon--was applied in low production of alpha/beta-interferon but high serum interferon. In low serum interferon and intact interferon reserves the treatment was combined: interferon inductor--cycloferon plus viferon. In all the children the above treatment was given following surgical (microendoscopic) removal of laryngeal

papillomas. The clinical course of laryngeal papillomatosis ran in accordance with changes of interferon status in the majority of cases.

Unique Identifier: 22051980

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*Magy Onkol 2002;46(1):35-41*

**[Causal association between human papilloma virus infection and head and neck and esophageal squamous cell carcinoma]**

[Article in Hungarian]

Szentirmay Z, Szanto I, Balint I, Polus K, Remenar E, Tamas L, Szentkuti G, Melegh Z, Nagy P, Kasler M.

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HPVs commonly cause proliferative lesions of squamous epithelium, and infection with certain HPV types carries a high risk of malignant transformation. We used molecular techniques to detect and type HPV in papillomas and carcinomas in the oral cavity and esophagus. DNA was extracted from 150 fresh or paraffin embedded biopsy specimens, and analyzed for HPV by PCR with 15 sets of consensus primers directed to conserved regions of L1 gene, three sets of HPV16E6 primers (specific for the HPV 16 prototype and L83V variant), and sets of primers specific for the E6 gene of other mucosa type HPVs including HPV 6, 11, 16, 18, 52, 58, 66 and 73. Overall, HPV sequences were detected in 61 of 150 specimens. HPV DNA sequences were detected in 16/32 specimens in the oropharyngeal region, in 13/36 specimens in larynx and 32/82 specimens in esophagus. Papillomas contained only the episomal form of HPV 16. In the esophagus, the most common type was HPV 73. In all specimens examined, HPV 6/11 (4/150), HPV 16 (23/150), HPV 35 (1/150), HPV 45 (1/150), HPV 54 (1/150), HPV 58 (1/150), HPV 61 (1/150), HPV 66 (1/150), HPV 68 (2/150), HPV 70 (3/150), HPV 72 (1/150), HPV 73 (16/150), double HPV infection (2/150), and unidentified HPV type (4/150) was detected. Interestingly, HPV was found in all verrucous carcinomas and in 18/22 basaloid squamous cell carcinomas. HPV16E6 T350G mutant were observed only in two of eight carcinomas. Using correspondence analysis, a segregation of specific virus types in specific clinico-pathologic lesions (verrucous carcinoma and basaloid squamous cell carcinoma) was proved. It was shown that the relative rates of the HPV positive tumors were significantly higher in women than in men. The synergic action of mucosal irritation and HPV infection may be necessary for the development of the papillomas and the specific types of carcinomas in the oral cavity and in the esophagus.

Unique Identifier: 22045824

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*J Virol* 2002 Jul;76(13):6453-9

**Intracutaneous DNA vaccination with the E8 gene of cottontail rabbit papillomavirus induces protective immunity against virus challenge in rabbits.**

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The cottontail rabbit papillomavirus (CRPV)-rabbit model has been used in several studies for testing prophylactic and therapeutic papillomavirus vaccines. Earlier observations had shown that the CRPV nonstructural genes E1, E2, and E6 induced strong to partial protective immunity against CRPV infection. In this study, we found that CRPV E8 immunization eliminated virus-induced papillomas in EIII/JC inbred rabbits (100%) and provided partial protection (55%) against virus challenge in outbred New Zealand White rabbits. CRPV-E8 is a small open reading frame, coding for a 50-amino-acid protein, that is colinear with the CRPV E6 gene and has features similar to those of the bovine papillomavirus and human papillomavirus E5 genes. Papillomas that grew on E8-vaccinated outbred rabbits were significantly smaller than those on vector-vaccinated rabbits ( $P < 0.01$ ; t test). Delayed-type hypersensitivity skin tests showed that some of the E8-vaccinated rabbits had positive responses to E8-specific peptides.

Unique Identifier: 22045622

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*Antivir Ther* 2002 Mar;7(1):1-9

**Therapy for recurrent respiratory papillomatosis.**

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Human papillomaviruses types 6 or 11 are aetiological agents of recurrent respiratory papillomatosis, a disease characterized by benign exophytic tumours usually on the vocal cords. Surgery debulks the tumours, but these growths generally recur at regular intervals. Adjunct medical treatments, aimed at containing the virus and growth of tumours, include indole-3-carbinol or its dimer diindolylmethane, interferon, photodynamic therapy and others. Preventive and therapeutic vaccines hold promise for eliminating the virus.

Unique Identifier: 22002441

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*Dis Colon Rectum* 2002 Apr;45(4):502-7

**Activity of HspE7, a novel immunotherapy, in patients with anogenital warts.**

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**PURPOSE:** Human papillomavirus causes anogenital squamous intraepithelial lesions, warts, and cancer. Treatment of squamous intraepithelial lesions to prevent cancer often requires extensive surgery. We tested a human papillomavirus-specific immunotherapy, HspE7, as a potential alternative. **METHODS:** HspE7 was constructed by fusing heat shock protein Hsp65 from bacille Calmette-Guerin to E7 protein from human papillomavirus-16. Improvement in pathologic diagnosis of patients with persistent high-grade squamous intraepithelial lesions was studied in an open-label trial (HspE7 500 microg monthly x3). Anogenital warts were not a trial parameter, but a retrospective review of the medical records of the first 22 patients enrolled at one site was undertaken to estimate the quality and frequency of responses of anogenital warts. Patients with warts by physical examination at baseline were scored at 24 weeks as to the percent reduction in wart size. **RESULTS:** Fourteen of the 22 patients had warts at baseline. At Week 24, 3 of the 14 patients had complete resolution of their warts, and 10 had warts reduced in size an estimated 70 to 95 percent. The remaining patient's warts increased in size. The reduction in size in most patients greatly diminished the procedure necessary for complete ablation. No serious or severe adverse events were related to HspE7. **CONCLUSIONS:** A retrospective review of patients' medical records suggests that HspE7 may be broadly active in anogenital warts. This activity crosses multiple human papillomavirus types. The warts improved substantially but usually did not totally disappear within six months. Patient follow-up continues. A new randomized, placebo-controlled trial is underway to evaluate these findings.

Unique Identifier: 22001124

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*Crit Rev Oral Biol Med* 2000;11(2):259-74

**Human papillomavirus infections in children: the potential role of maternal transmission.**

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To date, more than 100 types of human papillomavirus (HPV) have been identified. In the past 20 years, there has been an increasing interest in HPVs because of their potential role in the pathogenesis of malignant tumors. HPV infections are known to affect predominantly adult, sexually

active age groups, whereas skin warts, at various anatomic sites, are usually associated with younger individuals. The modes of viral transmission in children remain controversial, including perinatal transmission, auto- and hetero-inoculation, sexual abuse, and, possibly, indirect transmission via fomites. Recent studies on perinatal infection with HPV have been inconclusive. It is still unclear how frequently perinatal infection progresses to clinical lesions, whether genital, laryngeal, or oral. Conflicting reports have been published on the prevalence of HPV infections in children. The current consensus is, however, that newborn babies can be exposed to cervical HPV infection of the mother. The detection rate of HPV DNA in oral swabs of newborn babies varies from 4% to 87%. The concordance of HPV types detected in newborn babies and their mothers is in the range of 57% to 69%, indicating that the infants might acquire the HPV infection post-natally from a variety of sources. HPV antibodies have been detected in 10% to 57% of the children, and there is usually no correlation between seropositivity and the detection of HPV DNA in either the oral or the genital mucosa. There is also evidence that transmission in utero or post-natal acquisition is possible. The mode of in utero transmission remains unknown, but theoretically the virus could be acquired hematogenously, by semen at fertilization, or as an ascending infection in the mother. The understanding of viral transmission routes is important, particularly because several vaccination programs are being planned worldwide. The serologic response to HPV detected in different populations of young women or women at risk of cervical cancer might be due to genital infections, but the possibility that HPV infection has been acquired earlier in life through the oral mucosa or respiratory tract cannot be ruled out.

Unique Identifier: 21997496

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*Otolaryngol Head Neck Surg* 2002 Apr;126(4):333-48

### **Management of common voice problems: Committee report.**

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**OBJECTIVE:** This report provides the reader with a state-of-the-art update on a number of common voice problems that require phonosurgical intervention. **STUDY DESIGN AND SETTING:** This multiauthor review is not a position statement of the American Academy of Otolaryngology-Head and Neck Surgery (AAOHNS) and may reflect institutional preference and/or bias. It arose from a panel discussion at the AAOHNS meeting in 2000. **RESULTS:** We provide a review of the genesis and management of papillomatosis, dysplastic glottal epithelium, arytenoid granulomas, Reinke's edema, and vocal-fold paralysis. **CONCLUSIONS AND SIGNIFICANCE:** In the past decade, there has been a dramatic expansion of knowledge regarding a variety of voice disorders and associated treatment. There has been a convergence of basic

science investigations in anatomy, physiology, and pathology with clinical trials of treatment, both surgical and nonsurgical. This information should provide the reader with current insight into critical management issues of the aforementioned disorders.

Unique Identifier: 21993232

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*Cancer Lett* 2002 May 28;179(2):205-12

**Abrogation of IRF-1 response by high-risk HPV E7 protein in vivo.**

Um SJ, Rhyu JW, Kim EJ, Jeon KC, Hwang ES, Park JS.

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We have previously reported that human papillomavirus (HPV) E7 interacts with IRF-1, a key regulator of cellular immune response, and abrogates its transactivation function at the molecular level in vitro. To confirm our previous data, we investigated in vivo the E7-mediated down-regulation of IRF-1 using HPV E7-inducible cells and transgenic mice expressing HPV-18 E6/E7. When E7 was induced in the absence of tetracycline, the expression of target genes of IRF-1 (TAP-1, IFN-beta, MCP-1 that are important for cellular immunity) was clearly reduced as determined by RT-PCR. In addition, the IRF-1 activity was down-regulated in E7-expressing cells into which IFN-beta-CAT reporter plasmid was transfected. To further investigate the E7-mediated immune regulation in vivo, we constructed transgenic mice expressing E6 and E7 genes of HPV-18 under the control of HPV-18 promoter (URR). From several rounds of breeding, we obtained from a transgenic line that developed a cervical dysplasia and expressed E6/E7 as determined by histological examination and RT-PCR, respectively. Subsequent RT-PCR analysis indicated that TAP-1, IFN-beta, and MCP-1 genes were less expressed in a cervical tissue derived from transgenic mouse, when compared with a cervix derived from normal mouse. From these results, we conclude that the E7 transgene expression inactivates the transactivation function of IRF-1 in vivo, which might be important for the elucidation of the E7-mediated immune evading mechanism that is frequently found in cervical cancer.

Unique Identifier: 21885918

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*J Nutr* 2001 Dec;131(12):3294-302

**Indole-3-carbinol and diindolylmethane induce apoptosis of human cervical cancer cells and in murine HPV16-transgenic preneoplastic cervical epithelium.**

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Dietary indole-3-carbinol (I3C) has clinical benefits for both cervical cancer and laryngeal papillomatosis, and causes apoptosis of breast cancer cells *in vitro*. We asked whether I3C and its major acid-catalyzed condensation product diindolylmethane (DIM), which is produced in the stomach after consumption of cruciferous vegetables, could induce apoptosis of cervical cancer cell lines. We also asked whether this effect could be observed *in vivo*. *In vitro*, both I3C and DIM caused accumulation of DNA strand breaks in three cervical cancer cell lines. Induction of apoptosis was confirmed by nuclear morphology, nucleosome leakage, altered cytoplasmic membrane permeability and caspase 3 activation. Neither I3C nor DIM caused apoptotic changes in normal human keratinocytes. In C33A cervical cancer cells, DIM was more potent than I3C [dose at which the number of viable cells was 50% of that in untreated cultures (LD(50)) = 50-60 micromol/L for DIM and 200 micromol/L for I3C in a mitochondrial function assay] and faster acting. Furthermore, I3C reduced Bcl-2 protein in a time- and dose-dependent manner. In HPV16-transgenic mice, which develop cervical cancer after chronic estradiol exposure, apoptotic cells were detected in cervical epithelium by TdT-mediated dUTP nick-end labeling staining and by immunohistochemical staining of active caspase 3 only in mice exposed to 17beta-estradiol (E2) and fed I3C. Rare apoptotic cells were also observed by hematoxylin and eosin staining in the spinous layer of the cervical epithelium in both control and transgenic mice. Estradiol reduced the percentage of these late-stage apoptotic cells in the cervical epithelium of transgenic, E2-treated mice, but this reduction was prevented by I3C. These data confirm the proapoptotic action of I3C on transformed cells *in vitro*, extend the observations to cervical cancer cells and to DIM and show for the first time that dietary I3C results in increased apoptosis in target tissues *in vivo*.

Unique Identifier: 21602279

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